

HISMANAL (astemizole) Tablets

NOV 23 1998

NDA 19-402/S-014

Janssen Pharmaceuticals
1125 Trenton-Harbourton Road
Post Office Box 200
Titusville, NJ 08560-0200

Attention: Edward G. Brann
Manager, Regulatory Affairs

Dear Mr. Brann:

Please refer to your supplemental new drug application dated June 4, 1998, received June 9, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Hismanal (astemizole) Tablets.

We note that this supplement was submitted as a 'Special Supplement .Changes Being Effectuated' under 21 CFR 314.70(c).

This supplemental new drug application provides for revisions to the labeling to strengthen a contraindication regarding the use of Hismanal in patients with hepatic dysfunction. Your submission stated August 4, 1998, as the implementation date for the changes.

We have completed the review of this supplemental application and it is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted June 4, 1998).

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 19-402/S-014." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a Dear Health Care Practitioner letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

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MED WATCH, HF-2

FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Ms. Gretchen Trout, Project Manager, at (301) 827-1058.

Sincerely yours,

John K. Jenkins, M.D., F.C.C.P.
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

HISMANAL (astemizole) Tablets

WARNING BOX

QT PROLONGATION/VENTRICULAR ARRHYTHMIAS

RARE CASES OF SERIOUS CARDIOVASCULAR ADVERSE EVENTS INCLUDING DEATH, CARDIAC ARREST, QT PROLONGATION, TORSADES DE POINTES, AND OTHER VENTRICULAR ARRHYTHMIAS HAVE BEEN OBSERVED IN PATIENTS EXCEEDING RECOMMENDED DOSES OF ASTEMIZOLE. WHILE THE MAJORITY OF SUCH EVENTS HAVE OCCURRED FOLLOWING SUBSTANTIAL OVERDOSES OF ASTEMIZOLE, TORSADES DE POINTES (ARRHYTHMIAS) HAVE VERY RARELY OCCURRED AT REPORTED DOSES AS LOW AS 20-30 MG DAILY (2-3 TIMES THE RECOMMENDED DAILY DOSE). DATA SUGGEST THAT THESE EVENTS ARE ASSOCIATED WITH ELEVATION OF ASTEMIZOLE AND/OR ASTEMIZOLE METABOLITE LEVELS, RESULTING IN ELECTROCARDIOGRAPHIC QT PROLONGATION.

THESE EVENTS HAVE ALSO OCCURRED AT 10 MG DAILY IN A FEW PATIENTS WITH POSSIBLE AUGMENTING CIRCUMSTANCES (SEE CONTRAINDICATIONS AND WARNINGS). IN VIEW OF THE POTENTIAL FOR CARDIAC ARRHYTHMIAS, ADHERENCE TO THE RECOMMENDED DOSE SHOULD BE EMPHASIZED.

DO NOT EXCEED THE RECOMMENDED DOSE OF 10 MG (ONE TABLET) DAILY.

SOME PATIENTS APPEAR TO INCREASE THE DOSE OF HISMANAL (ASTEMIZOLE) TABLETS IN AN ATTEMPT TO ACCELERATE THE ONSET OF ACTION. PATIENTS SHOULD BE ADVISED NOT TO DO THIS AND NOT TO USE HISMANAL® ON AN AS-NEEDED BASIS (I.E., P R N) FOR IMMEDIATE RELIEF OF SYMPTOMS.

CONCOMITANT ADMINISTRATION OF ASTEMIZOLE WITH SYSTEMIC KETOCONAZOLE, TRACONAZOLE, ERYTHROMYCIN, CLARITHROMYCIN, TROLEANDOMYCIN, MIBEFRADIL OR QUININE IS CONTRAINDICATED (SEE CONTRAINDICATIONS AND PRECAUTIONS: DRUG INTERACTIONS).

SINCE ASTEMIZOLE IS EXTENSIVELY METABOLIZED BY THE LIVER, THE USE OF ASTEMIZOLE IN PATIENTS WITH HEPATIC DYSFUNCTION IS CONTRAINDICATED.

IN SOME CASES, SEVERE ARRHYTHMIAS HAVE BEEN PRECEDED BY EPISODES OF SYNCOPE. SYNCOPE IN PATIENTS RECEIVING ASTEMIZOLE SHOULD LEAD TO IMMEDIATE DISCONTINUATION OF TREATMENT AND APPROPRIATE CLINICAL EVALUATION, INCLUDING ELECTRO-CARDIOGRAPHIC TESTING (LOOKING FOR QT PROLONGATION AND VENTRICULAR ARRHYTHMIA).

(SEE CLINICAL PHARMACOLOGY, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, OVERDOSAGE, AND DOSAGE AND ADMINISTRATION.)

HISMANAL (astemizole) Tablets

DESCRIPTION

HISMANAL (astemizole) is a histamine H₁-receptor antagonist available in scored white tablets for oral use. Each tablet contains 10 mg of astemizole, and, as inactive ingredients: lactose, cornstarch, microcrystalline cellulose, pregelatinized starch, povidone K90, magnesium stearate, colloidal silicon dioxide, and sodium lauryl sulfate. Astemizole is chemically designated as 1 -[(4-fluorophenyl)-methyl]-N-[1 -[2- (4-methoxyphenyl)ethyl]-4 -piperidiny]-1H-benzimidazol-2-amine, with a molecular weight of 458.58. The empirical formula is C₂₈H₃₁FN₄O. The structural formula of astemizole is:

[Chemical structure to be inserted here.]

Astemizole is a white to slightly off-white powder; it is insoluble in water, slightly soluble in ethanol and soluble in chloroform and methanol.

CLINICAL PHARMACOLOGY

Mechanism of Action

Astemizole is a long-acting, selective histamine H₁-receptor antagonist. Receptor binding studies in animals demonstrated that at pharmacological doses, astemizole occupies peripheral H₁-receptors but does not reach H₁-receptors in the brain. Whole body autoradiographic studies in rats, radiolabel tissue distribution studies in dogs and radioligand binding studies of guinea pig brain H₁-receptors have shown that astemizole does not readily cross the blood-brain barrier. Screening studies in rats at effective antihistaminic doses showed no anticholinergic effects. Studies in humans using the recommended dosage regimens have not been performed to determine whether astemizole is associated with a different frequency of anticholinergic effects than therapeutic doses of other antihistamines.

Pharmacokinetics

The absorption of astemizole is reduced by 60% when taken with meals. In single oral dose studies, astemizole was rapidly absorbed from the gastrointestinal tract; peak plasma concentrations of unchanged astemizole were reached within one hour. Due to extensive first pass metabolism and significant tissue distribution, plasma concentrations of unchanged drug were low. Elimination of unchanged astemizole occurred with a half-life of approximately one day. Elimination of astemizole plus hydroxylated metabolites, considered together to represent the pharmacologically active fraction in plasma, was biphasic with half-lives of 20

HISMANAL (astemizole) Tablets

hours for the distribution phase and 7-11 days for the elimination phase. The pharmacokinetics of astemizole plus hydroxylated metabolites are dose proportional following single doses of 10 to 30 mg.

Following chronic administration, steady state plasma concentrations of astemizole plus hydroxylated metabolites (mainly desmethylastemizole) were reached within four to eight weeks; concentrations of the metabolites are substantially higher than those of unchanged astemizole. Astemizole plus hydroxylated metabolites decayed biphasically with an initial half-life of 7-9 days, with plasma concentrations being reduced by 75% within this phase, and with a terminal half-life of about 19 days. The initial phase ($t_{1/2}$ =7-9 days) appears to determine the time to reach steady state plasma concentrations of astemizole plus hydroxylated metabolites. Steady state plasma concentrations of unchanged astemizole were reached by 6 days (with a range of 6-9 days); unchanged astemizole was eliminated from plasma with a half-life of approximately 2 days (with a range of 1-2.5 days).

The in-vitro plasma protein binding of unchanged astemizole (100 ng/mL) as 96.7% with 2.3% being found as free drug in the plasma water. In human blood with an astemizole concentration of 100 ng/mL, 61.5% of astemizole was bound to the plasma proteins, with 36.2% being distributed to the blood cell fraction. The concentration of astemizole found in the blood was the same as that found in the plasma fraction of the blood. Binding studies for the astemizole metabolite(s) which achieve much higher concentrations than astemizole under chronic dosing conditions have not been conducted.

Metabolism

Excretion and metabolism studies with ^{14}C -labeled astemizole in volunteers demonstrated that the drug is almost completely metabolized and primarily excreted in the feces.

In-vitro metabolism studies with human liver microsomes indicate that astemizole is metabolized to its principle circulating metabolite, desmethylastemizole, predominantly by a specific cytochrome P-450 isozyme, CYP 3A4. These in-vitro studies also indicate that the P-450 isozymes CYP 1 A2 and CYP 2D6 are involved in the minor metabolic pathways of astemizole. The relative contributions of the CYP 3A4 isozymes in the liver and gastrointestinal mucosa to the presystemic clearance of astemizole are unknown. Concurrent administration of astemizole with the CYP 3A4 inhibitors ketoconazole or erythromycin to healthy volunteers was associated with significantly increased plasma concentrations of astemizole. (See WARNING BOX; CONTRAINDICATIONS; WARNINGS; PRECAUTIONS, Drug Interactions; ADVERSE REACTIONS; and DOSAGE AND ADMINISTRATION.)

Special Populations

Elevated levels of unmetabolized astemizole, whether due to hepatic dysfunction, concomitant use of interacting medications, or overdose, have been associated with QTC interval prolongation and serious cardiac events. (See WARNING BOX; CONTRAINDICATIONS; WARNINGS; PRECAUTIONS, Drug Interactions; ADVERSE REACTIONS;

and DOSAGE AND ADMINISTRATION.)

Hepatically Impaired

In a study involving sixteen subjects with mild or moderate hepatic impairment as determined by Pugh's classification, the mean AUC and Cmax of unmetabolized astemizole showed clinically significant increases in subjects with hepatic impairment compared to eight subjects with normal hepatic function. The use of HISMANAL in patients with hepatic dysfunction is contraindicated. (See WARNING BOX, CONTRAINDICATIONS, PRECAUTIONS and DOSAGE AND ADMINISTRATION.)

Systematic evaluation of the pharmacokinetics in patients with renal dysfunction has not been performed.

Effects on Cardiac Repolarization

In controlled clinical trials, small mean increases from baseline in corrected QT interval (QTC) of approximately 7 milliseconds were observed at daily doses of 10 mg.

Clinical Trials

Seasonal Allergic Rhinitis

Clinical trials supporting the approval of HISMANAL (astemizole) Tablets for seasonal allergic rhinitis involved 425 patients aged 12 and over who received either HISMANAL® once daily or another antihistamine and/or placebo in double-blind randomized controlled studies. HISMANAL was superior to placebo in effects on nasal and non-nasal symptoms of seasonal allergic rhinitis. In these and other clinical studies, the efficacy of HISMANAL versus placebo was not demonstrated until several days after beginning dosing.

Idiopathic Chronic Urticaria

Clinical trials supporting the approval of HISMANAL for idiopathic chronic urticaria involved 142 patients aged 12 and over who received either HISMANAL® once daily or another antihistamine and/or placebo in double-blind randomized controlled studies. HISMANAL® was superior to placebo in the management of idiopathic chronic urticaria as demonstrated by reduction in associated itching, erythema, and hives. The onset of efficacy of HISMANAL® versus placebo in this condition has not been adequately studied.

INDICATIONS AND USAGE

HISMANAL® (astemizole) Tablets are indicated for the relief of symptoms associated with seasonal allergic rhinitis and chronic idiopathic urticaria. HISMANAL® should not be used on an as-needed (i.e., p r n) basis for immediate relief of symptoms. Patients should be advised

not to increase the dose in an attempt to accelerate the onset of action.

Clinical studies have not been conducted to evaluate the effectiveness of HISMANAL® in the common cold.

CONTRAINDICATIONS

CONCOMITANT ADMINISTRATION OF ASTEMIZOLE WITH SYSTEMIC KETOCONAZOLE, ITRACONAZOLE, ERYTHROMYCIN, CLARITHROMYCIN, TROLEANDOMYCIN, MIBEFRADIL DIHYDROCHLORIDE OR QUININE IS CONTRAINDICATED. ASTEMIZOLE IS ALSO CONTRAINDICATED IN PATIENTS WITH HEPATIC DYSFUNCTION OR WHO ARE TAKING OTHER CONCOMITANT MEDICATIONS KNOWN TO IMPAIR ITS METABOLISM. QT PROLONGATION HAS BEEN DEMONSTRATED IN PATIENTS TAKING ASTEMIZOLE IN THESE SETTINGS AND CASES OF SERIOUS CARDIOVASCULAR EVENTS, INCLUDING DEATH, CARDIAC ARREST, AND TORSADES DE POINTES, HAVE BEEN REPORTED IN THESE PATIENT POPULATIONS. (See WARNING BOX; WARNINGS; PRECAUTIONS, Special Populations; PRECAUTIONS, Drug Interactions; ADVERSE REACTIONS; and DOSAGE AND ADMINISTRATION.)

HISMANAL® is contraindicated in patients with known hypersensitivity to astemizole or any of the inactive ingredients.

WARNINGS

Astemizole undergoes extensive presystemic metabolism to its major active metabolite predominantly by the cytochrome P-450 3A4 isozyme. Cytochromes P-450 1A2 and 2D6 contribute to the overall metabolism of astemizole to a lesser extent. These metabolic pathways may be impaired in patients with hepatic dysfunction (e.g., alcoholic cirrhosis, hepatitis) or who are taking drugs systemically such as ketoconazole, itraconazole, erythromycin, clarithromycin, troleandomycin, mibefradil dihydrochloride, other potent inhibitors of this isozyme or quinine. Interference with this metabolism can lead to elevated astemizole and/or desmethylastemizole plasma levels associated with QT prolongation and increased risk of ventricular tachyarrhythmias (such as torsades de pointes, ventricular tachycardia, and ventricular fibrillation) at the recommended dose. HISMANAL® (astemizole) Tablets are contraindicated for use by patients with these conditions. (See WARNING BOX; CONTRAINDICATIONS; PRECAUTIONS, Special Populations; PRECAUTIONS, Drug Interactions; and DOSAGE AND ADMINISTRATION.)

Patients known to have conditions leading to QT prolongation may experience QT prolongation and/or ventricular arrhythmia with astemizole at recommended doses. The effect of astemizole in patients who are receiving other agents which alter the QT interval is unknown. However, in view of astemizole's known potential for QT prolongation, it is advisable to avoid its use in 1) patients with congenital QT prolongation syndrome, 2) those taking medications which are reported to prolong QT intervals (including certain antiarrhythmics, bepridil, certain psychotropics, cisapride, sparfloxacin or terfenadine [this list may not be all inclusive]), 3) patients with electrolyte abnormalities such as hypokalemia or

hypomagnesemia, or 4) those taking diuretics with the potential for inducing electrolyte abnormalities.

The relationship of underlying cardiac disease to the development of ventricular tachyarrhythmias while on HISMANAL® therapy is unclear; nonetheless, HISMANAL® should also be used with caution in these patients.

PRECAUTIONS

General

Elevated concentrations of astemizole and/or its principal metabolite, desmethylastemizole, whether due to overdose, hepatic dysfunction, or concomitant medications, have been associated with altered cardiac repolarization and/or serious cardiac arrhythmias.

Patients with impaired hepatic function or those receiving treatment with significant inhibitors of CYP 3A4 or quinine may experience QT prolongation and/or ventricular arrhythmias, including torsades de pointes, at the recommended dose. Patients having conditions leading to QT prolongation may also be at risk for these cardiovascular events. (See WARNING

BOX; CLINICAL PHARMACOLOGY; CONTRAINDICATIONS; WARNINGS; PRECAUTIONS, Special Populations; PRECAUTIONS, Drug Interactions; ADVERSE REACTIONS; and DOSAGE AND ADMINISTRATION.)

Rare cases of anaphylaxis, including anaphylactic shock, have been reported. Caution should also be used when treating patients with renal impairment.

Information for Patients

Patients taking HISMANAL® (astemizole) Tablets should receive the following information and instructions. Antihistamines are prescribed to reduce allergic symptoms. Patients taking HISMANAL® should be advised 1) to adhere to the recommended dose, and 2) that the use of excessive doses may lead to serious cardiovascular events. Some patients appear to increase the dose of HISMANAL in an attempt to accelerate the onset of action. PATIENTS SHOULD BE ADVISED NOT TO DO THIS and not to use HISMANAL® on an as-needed (i.e., prn) basis for immediate relief of symptoms. Patients should be questioned about use of any other prescriptions or over-the-counter medication, and should be cautioned regarding the potential for life-threatening arrhythmias with concurrent use of ketoconazole, itraconazole, erythromycin, clarithromycin, troleandomycin, mibefradil dihydrochloride, or quinine. Limited human data indicate that although beverages containing quinine (up to 80 mg/day or about 32 ounces of tonic water) may elevate plasma levels of astemizole and desmethylastemizole, this effect is small and is not accompanied by significant prolongation of the QT interval. Patients should be advised to consult their physician before concurrent use of other medications with astemizole. Patients should also be advised that HISMANAL® should not be taken with grapefruit juice. Patients should be questioned about pregnancy or lactation before starting HISMANAL® therapy, since the drug should be used in pregnancy or lactation only if the potential benefit justifies the potential risk to fetus or baby (see Pregnancy

subsection). In addition, patients should be instructed to take HISMANAL on an empty stomach, e.g., at least 2 hours after a meal. No additional food should be taken for at least 1 hour after dosing. Patients should also be instructed to store this medication in a tightly closed container in a cool, dry place, away from heat or direct sunlight, and away from children.

Drug Interactions

Before prescribing or adding a newly available drug to the regimen of a patient receiving astemizole, the package insert of the new drug and/or the medical literature should be consulted to determine if an interaction between the new drug and astemizole has been reported.

Astemizole is predominantly metabolized by the cytochrome P-450 3A4 (CYP 3A4) isozyme with some metabolism by the 1A2 and 2D6 isozymes. Inhibition of CYP 3A4 in patients taking HISMANAL® can result in markedly elevated plasma concentrations of astemizole and/or its principal metabolite, desmethylastemizole. This could increase or prolong both the therapeutic effect and adverse events. Presence of elevated astemizole/desmethylastemizole concentrations is associated with significant prolongation of the QT and QTC intervals. (See BOX WARNING; CONTRAINDICATIONS; WARNINGS; PRECAUTIONS, Drug Interactions; ADVERSE REACTIONS; and DOSAGE AND ADMINISTRATION.)

Concomitant administration of the drugs in Table A with astemizole is contraindicated.

Table A

Drugs Contraindicated for Use

with Astemizole

| |
|---|
| Azole antifungals: ketoconazole, itraconazole |
| Macrolide antibiotics: clarithromycin, erythromycin, troleandomycin |
| Other: mibefradil, quinine |

The drugs noted below have been demonstrated to be inhibitors of CYP 3A4 in-vitro and have been shown to have clinically significant pharmacokinetic interactions with other substrates of this isozyme. Because of the potential for these drugs to influence the metabolism of astemizole and until the clinical significance of these findings is fully established, concomitant use of astemizole with the drugs in Table B is not recommended.

Table B

Drugs Not Recommended for Use

with Astemizole

Other antifungals: fluconazole, metronidazole, miconazole i.v.

Serotonin Reuptake Inhibitors (SRI): fluoxetine, fluvoxamine, nefazodone, paroxetine, sertraline

HIV Protease Inhibitors: ritonavir, indinavir, saquinavir, nelfinavir

Other: grapefruit juice, zileuton, other potent CYP 3A4 inhibitors

Ketoconazole/Itraconazole

Concomitant administration of ketoconazole or itraconazole with astemizole results in markedly elevated concentrations of astemizole and its principal metabolite, desmethylastemizole. Therefore, concomitant administration of HISMANAL with ketoconazole or itraconazole is contraindicated.

Other Antifungals

Due to the chemical similarity of fluconazole, metronidazole, and miconazole i.v. to ketoconazole, concomitant use of these products with astemizole is not recommended.

Macrolide Antibiotics

Concomitant administration of erythromycin with astemizole results in markedly elevated concentrations of astemizole and its principal metabolite, desmethylastemizole. Because of the chemical similarity of clarithromycin and troleandomycin to erythromycin and the known relative inhibitory potencies of these macrolides, concomitant administration of erythromycin, clarithromycin or troleandomycin with astemizole is also contraindicated.

Mibefradil dihydrochloride

Mibefradil is an inhibitor of the P-450 isozyme primarily responsible for the metabolism of astemizole (CYP 3A4). Coadministration of mibefradil with terfenadine (also metabolized by CYP 3A4) in healthy subjects results in inhibition of terfenadine metabolism and accumulation of unmetabolized terfenadine with resulting clinically significant repolarization abnormalities. Because of the potential for mibefradil to influence the metabolism of astemizole, concomitant use of astemizole with mibefradil dihydrochloride is contraindicated.

Quinine

Although quinine is not known to be an inhibitor of CYP 3A4, concomitant administration of quinine with astemizole results in markedly elevated concentrations of astemizole and its principal metabolite, desmethylastemizole. The mechanism of this interaction is not known. Concomitant administration of astemizole with quinine is therefore contraindicated.

Other 3A4 Inhibitors

Astemizole is metabolized by the cytochrome P-450 3A4 isozyme (CYP 3A4). Inhibition of this enzyme in patients taking HISMANAL® results in increased plasma concentrations of astemizole and/or its principal metabolite, desmethylastemizole. Presence of elevated astemizole/desmethylastemizole concentrations is associated with significant prolongation of the QT and QTC intervals. The drugs noted below have been demonstrated to be inhibitors of CYP 3A4 in-vitro and have been shown to have clinically significant pharmacokinetic interactions with other substrates of this isozyme. Because of the potential for these drugs to influence the metabolism of astemizole and until the clinical significance is fully established, concomitant use of astemizole and the drugs below is not recommended.

Serotonin Reuptake Inhibitors: fluoxetine, fluvoxamine, nefazodone, paroxetine, sertraline

HIV Protease Inhibitors: ritonavir, indinavir, saquinavir, nelfinavir

Grapefruit juice

Zileuton

Other potent CYP 3A4 inhibitors

Carcinogenesis, Mutagenesis, Impairment of Fertility

Astemizole did not reveal any carcinogenic potential at oral doses up to 80 mg/kg/day for 24 months in rats and 18 months in mice (approximately 65 and 30 times, respectively, the maximum recommended daily oral dose in adults on a mg/in² basis). Micronucleus, dominant lethal, sister chromatid exchange and Ames tests of astemizole have not revealed mutagenic activity. No impairment of fertility was observed in rats at oral doses up to 40 mg/kg/day (approximately 30 times the maximum recommended daily oral dose in adults on a mg/m² basis).

Pregnancy: Pregnancy Category C

Teratogenic effects were not observed in rats at oral doses up to 160 mg/kg/day (approximately 130 times the maximum recommended daily oral dose in adults on a mg/m² basis) and in rabbits at oral doses up to 40 mg/kg/day (approximately 65 times the maximum recommended daily oral dose in adults on a mg/m² basis). Maternal mortality was seen in rabbits at oral doses of 10 mg/kg/day and above (approximately 16 times the maximum recommended daily oral dose in adults on a mg/m² basis). Embryocidal effects accompanied by maternal effects were observed in rats at oral doses of 40 mg/kg/day and above (approximately 30 times the maximum recommended daily oral dose in adults on a mg/m² basis). Embryotoxicity was not observed in rats at an oral dose of 10 mg/kg/day (approximately 8 times the maximum recommended daily oral dose in adults on a mg/m² basis) and maternal toxicity was not reported in rabbits at an oral dose of 2.5 mg/kg/day (approximately 4 times the maximum recommended daily oral dose in adults on a mg/m² basis). There are no adequate and well-controlled studies in pregnant women. HISMANAL® should be used during pregnancy only if the potential benefit justifies the potential risk to the

fetus. Metabolites may remain in the body for as long as 4 months after the end of dosing, calculated on the basis of 6 times the terminal half-life (see CLINICAL PHARMACOLOGY section).

Nursing Mothers

Astemizole is excreted in the milk of dogs. It is not known whether astemizole is excreted in human milk. Because certain drugs are known to be excreted in human milk, caution should be exercised when HISMANAL® is administered to a nursing woman.

Pediatric Use

Safety and efficacy in children under 12 years of age have not been demonstrated.

ADVERSE REACTIONS

Cardiovascular Adverse Events

Rare reports of serious cardiovascular effects have been received which include ventricular tachyarrhythmias (torsades de pointes, ventricular tachycardia, ventricular fibrillation, and cardiac arrest), hypotension, syncope, and dizziness. Rare reports of deaths resulting from ventricular tachyarrhythmias have been received. In most instances, astemizole overdoses, QT-prolonging conditions, drug interactions leading to impaired astemizole metabolism or other factors which could have contributed to the events, were observed. (See WARNING BOX; CONTRAINDICATIONS; WARNINGS; PRECAUTIONS, Drug Interactions; and DOSAGE AND ADMINISTRATION.) Hypotension, palpitations, syncope, and dizziness could reflect undetected ventricular arrhythmia. IN SOME PATIENTS, DEATH, CARDIAC ARREST, OR TORSADES DE POINTES HAVE BEEN PRECEDED BY EPISODES OF SYNCOPE (see WARNINGS). Rare reports of serious cardiovascular adverse events have been received, some involving QT prolongation and torsades de pointes, in apparently normal individuals without identifiable risk factors and at recommended doses. There is not conclusive evidence of a causal relationship of these events with astemizole.

Reports of serious cardiovascular effects associated with patients intentionally taking more

than the recommended daily dose of astemizole in an attempt to accelerate the onset of action have been received. Patients should be cautioned not to exceed the recommended daily dose (see PRECAUTIONS, Information for Patients).

General Adverse Events

The reported incidences of adverse reactions listed in the following table are derived from controlled clinical studies in adults. In these studies the usual maintenance dose of HISMANAL® (astemizole) Tablets was 10 mg once daily.

| ADVERSE EVENT | Percent of Patients Reporting | | |
|----------------------------|-------------------------------|----------------------|---------------------------------|
| | Controlled Studies | | ACTIVE** CONTROLS (N=304) |
| | HISMANAL (N=1 630) | PLACEBO (N=1 109) | |
| Central Nervous System | | | |
| Drowsiness | 7.1 | 6.4 | 22.0 |
| Headache | 6.7 | 9.2 | 3.3 |
| Fatigue | 4.2 | 1.6 | 11.8 |
| Appetite increase | 3.9 | 1.4 | 0.0 |
| Weight increase | 3.6 | 0.7 | 1.0 |
| Nervousness | 2.1 | 1.2 | 0.3 |
| Dizziness | 2.0 | 1.8 | 1.0 |
| Gastrointestinal System | | | |
| Nausea | 2.5 | 2.9 | 1.3 |
| Diarrhea | 1.8 | 2.0 | 0.7 |
| Abdominal pain | 1.4 | 1.2 | 0.7 |
| Eye, Ear, Nose, and Throat | | | |
| Mouth dry | 5.2 | 3.8 | 7.9 |
| Pharyngitis | 1.7 | 2.3 | 0.3 |
| Conjunctivitis | 1.2 | 1.2 | 0.7 |
| Other | | | |
| Arthralgia | 1.2 | 1.6 | 0.0 |

*Duration of treatment in controlled studies ranged from 7 to 182 days

**Active Controls: Clemastine (N=1 37); Chlorpheniramine (N=100); Pheniramine Maleate (N=47); d-Chlorpheniramine (N=20)

Adverse reaction information has been obtained from more than 7500 patients in all clinical trials. Weight gain has been reported in 3.6% of astemizole treated patients involved in controlled studies, with an average treatment duration of 53 days. In 46 of the 59 patients for whom actual weight gain data was available, the average weight gain was 3.2 kg.

Less frequently occurring adverse experiences reported in clinical trials or spontaneously from marketing experience with HISMANAL® include: angioedema, asymptomatic liver enzyme elevations, bronchospasm, depression, edema, epistaxis, hepatitis, myalgia, palpitation, paresthesia, photosensitivity, pruritus, and rash.

Rare cases of anaphylaxis, including anaphylactic shock, have been reported.

Marketing experiences include isolated cases of convulsions. A causal relationship with HISMANAL® has not been established.

OVERDOSAGE

In the event of overdose, supportive measures including gastric lavage and emesis should be employed. Substantial overdoses of HISMANAL (astemizole) Tablets can cause death, cardiac arrest, QT prolongation, torsades de pointes, and other ventricular arrhythmias. These events can also occur, although rarely, at doses (20-30 mg) close to the recommended dose (10 mg/daily). Patients should be advised not to take more than the daily recommended dose of HISMANAL in attempts to accelerate the onset of action. (See WARNING BOX; CONTRAINDICATIONS; WARNINGS; PRECAUTIONS, Information for Patients; PRECAUTIONS, Drug Interactions; ADVERSE REACTIONS; and DOSAGE AND ADMINISTRATION.)

Seizures and syncope have also been reported with overdose and may be associated with a cardiac event.

Overdose patients should be carefully monitored as long as the QT interval is prolonged or arrhythmias are present. In some cases, this has been up to six days. In overdose cases in

which ventricular arrhythmias are associated with significant QT prolongation, treatment with antiarrhythmics known to prolong QT intervals is not recommended. Astemizole does not appear to be dialyzable.

Oral median lethal doses for astemizole were 2052 mg/kg in mice (approximately 830 times the maximum recommended daily oral dose in adults on a mg/m² basis) and 3154 mg/kg in rats (approximately 2600 times the maximum recommended daily oral dose in adults on a mg/m² basis). In neonatal rats, the oral median lethal dose was 1070 mg/kg (approximately 870 times the maximum recommended daily oral dose in adults on a mg/m² basis).

DOSAGE AND ADMINISTRATION

The recommended dosage for adults and children 12 years of age and older is 10 mg (1 tablet) once daily.

DO NOT EXCEED THE RECOMMENDED DOSE. Patients should be advised not to increase the dose of HISMANAL® (astemizole) Tablets in an attempt to accelerate the onset of action. **USE OF HISMANAL IN PATIENTS WITH HEPATIC DYSFUNCTION OR IN PATIENTS TAKING KETOCONAZOLE, ITRACONAZOLE, ERYTHROMYCIN, CLARITHROMYCIN, TROLEANDOMYCIN, MIBEFRADIL DIHYDROCHLORIDE, OR QUININE IS CONTRAINDICATED.** (See WARNING BOX; CONTRAINDICATIONS; WARNINGS; PRECAUTIONS, Information for Patients; PRECAUTIONS, Drug Interactions; ADVERSE REACTIONS; OVERDOSAGE; and DOSAGE AND ADMINISTRATION.)

Studies evaluating the need for dosage adjustments for patients with renal dysfunction have not been performed. Since astemizole is extensively metabolized by the liver, use of HISMANAL in patients with hepatic dysfunction is contraindicated.

HISMANAL® should be taken on an empty stomach, e.g., at least two hours after a meal. There should be no additional food intake for at least one hour post-dosing.

HISMANAL® (astemizole) Tablets are available as white, scored tablets containing 10 mg of astemizole debossed "JANSSEN" and on the reverse side debossed "Ast/10".

NDC 50458-510-10 (HDPE bottles of 100 tablets)
/

NDC 50458-510-13 (HDPE bottles of 30 tablets with a child resistant closure)

Store at controlled room temperature 59°-77°F (15°C-25°C).

Protect from moisture.

U.S. Patent 4,219,559

Revised January 1998, June 1998

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